The Association of Endometriosis and Phthalate Exposure: A Meta-Analysis of Observational Studies

Pi-I Debby Lin-Mruk, MS  
Doctoral Candidate  
Harvard TH Chan School of Public Health

NEEP 2015  
Occupational / Environmental Health Session  
Oct 1st, 2015 (3:45pm-5:00pm Livingston 4)

---

Endometriosis  
- hormone-dependent inflammatory condition

---

Exposure to Phthalate  
- may affect reproductive function

---

Phthalate  
- it's all around us

---
Research Aim

Endometriosis patients

Elevated phthalate metabolites

Observational Studies

True Association?

Search Criteria and Eligibility Criteria

- PubMed/MEDLINE and EMBASE (upto September 16th, 2015)
- MeSH term
  - 'endometriosis'[MeSH Terms] OR 'endometriosis'[All Fields]
  - AND ('phthalic acid'[Supplementary Concept]
    OR 'phthalic acid'[All Fields] OR 'phthalate'[All Fields])
- Inclusion criteria
  1. case-control studies
  2. be conducted on human adults
  3. have urinary phthalate metabolites as the exposure measurement (must have urinary MEHP concentration)
  4. have endometriosis as the outcome
  5. report mean and standard deviation or standard error of the effect estimate

Research Method

- Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group Reporting format

Data Extraction

- 3 reviewers independently extracted data using standardized form
  - For data analysis
    - year of publication
    - study design
    - study population
    - study size
    - exposure chemical
    - sample type
    - exposure level
    - OR and 95% CI
    - description of interpretation of odds
    - outcome measurement methods
    - controlled variables
  - For quality of publication
    - definition and description of cases and controls
    - non-response rate
    - description and definition of exposure measurement
Data Synthesis

- OR of the highest exposure group compared to the lowest exposure group
- Continuous exposure
  - Use median and geometric mean of the urinary MEHP concentration of the total population and converted exposure to dichotomous variable

Studies Included in Meta-Analysis

<table>
<thead>
<tr>
<th>Study (Location)</th>
<th>Case Exposed</th>
<th>Control Exposed</th>
<th>Exposure MEHP (ug/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upson (2013) USA</td>
<td>92/189</td>
<td>92</td>
<td>0.2</td>
</tr>
<tr>
<td>Louis et al. (2012) USA (Operative cohort)</td>
<td>190/263</td>
<td>8.1</td>
<td></td>
</tr>
<tr>
<td>(Population cohort)</td>
<td>14/133</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weert et al. (2009) USA</td>
<td>87/1026</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Burke et al. (2001) Japan</td>
<td>57/50</td>
<td>7.8 (SD of the method)</td>
<td></td>
</tr>
<tr>
<td>Huang et al. (2010) Taiwan</td>
<td>28/20</td>
<td>1.10</td>
<td></td>
</tr>
</tbody>
</table>

Measurement method
- Exposure
  - SPE
- HPLC-MS/MS
- Outcome
  - Surgical visualization
  - Laparoscopy result
  - Pathological results

Assessment of Study Quality

- Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upson et al., 2013</td>
<td>☆☆☆☆☆</td>
<td>☆☆☆</td>
<td>☆☆☆☆☆</td>
</tr>
<tr>
<td>Buck Louis et al., 2013 (population cohort)</td>
<td>☆☆☆☆</td>
<td>☆☆☆☆☆</td>
<td>☆☆☆☆☆</td>
</tr>
<tr>
<td>Buck Louis et al., 2013 (Operative cohort)</td>
<td>☆☆☆☆</td>
<td>☆☆☆☆☆</td>
<td>☆☆☆☆☆</td>
</tr>
<tr>
<td>Moore et al., 2010</td>
<td>☆☆☆☆</td>
<td>☆☆☆☆☆</td>
<td>☆☆☆☆☆</td>
</tr>
<tr>
<td>Ishi et al., 2009</td>
<td>☆☆</td>
<td>☆☆☆☆☆</td>
<td>☆☆☆☆☆</td>
</tr>
<tr>
<td>Huang et al., 2010</td>
<td>☆☆☆</td>
<td>☆☆☆☆☆</td>
<td>☆☆☆☆☆</td>
</tr>
</tbody>
</table>
### Introduction

#### Method

- Meta-regression to evaluate different sources of heterogeneity
  - Study country
  - Study size
  - Exposure range

  The OR of endometriosis for studies taken place among the US population was lower than those among Asian countries by a factor of 0.5721 (p=0.543).

#### Result

- Diagnostic methods for endometriosis may partially account for the variation among the results of the included studies.
- One study recruited subjects from infertility clinic → selection bias.

#### Discussion

- **Study limitation?**
  - MEHP has short half life (excrete within 1–4 hours)
  - Limit the ability to study long term effect of phthalate exposure
  - Other subspecies of phthalate ester acid
  - Highly correlated
  - Non-linear association
  - Simple dichotomous method cannot capture the trend
What did we find?

- No association between urinary MEHP level and endometriosis was found by meta-analysis.
- However, we could not rule out the risk on reproductive health from phthalate exposure, considering the study the limitations.

Questions?

Additional slides

Statistical Analysis

- Random-effects model
- Heterogeneity:
  - Standard P test
  - meta-regression
  - subgroup analysis
- geographical location, the number of cases and controls, and the range of phthalate exposure
- Sensitivity analysis
- Funnel plot to assess publication bias
- Egger's regression test to test for asymmetry
Sensitivity analysis

Funnel Plot for Assessing Publication Bias